Abstract

It is presently accepted that the mechanism of action for all anti-tumor tubulin ligands involves the perturbation of microtubule dynamics during the G2/M phase of cell division and subsequent entry into apoptosis (1). In this invention, we report a novel tubulin ligands which have a unique mechanism of action. These compounds,. halogenated derivatives of acetamido benzoyl ethyl ester (HAABE), arrest cancer cells in S-phase and cause cell death by a combination of apoptosis (DNA ladder) and necrosis (DNA degradation) type mechanisms. Normal cells are not affected at the same concentrations of compound. The ligands bind covalently to tubulin in vitro and in vivo and shows potent cancericidal activity in tissue culture assays and in animal tumor models. These compounds target early S-phase at the G1/S transition rather than the G2/M phase and mitotic arrest. Bcl-2 phosphorylation, a marker of mitotic microtubule inhibition by other tubulin ligands was dramatically altered, phosphorylation was rapid and biphasic rather than a slow linear event. The halogenated ethyl ester series of derivatives thus constitute a unique set of tubulin ligands which induce a novel mechanism of cancer cell death.